Notice of Allowability	Application No. 10/003,837	Applicant(s) PECK ET AL.	
	Examin r Tiffany A Fetzner	Art Unit 2859	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *05/24/2004*.
2. ☐ The allowed claim(s) is/are *38 and 39*.
3. ☒ The drawings filed on *20 June 2002* are accepted by the Examiner.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
   1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☒ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *06/01/2004*.
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Oth r _____.

Examiner's Amendment

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

2. Authorization for this examiner's amendment, along with authorization to charge any necessary additional fees, was given in a telephone interview with **Attorney Peter D. McDermott Reg. No. 29,411** on June 1st 2004. [See the examiner's Interview Summary which accompanies this office action.]

3. The application has been amended as follows:

In the **After-Final Amendment of May 24th 2004**, which has been marked **Okay to Enter** by the examiner:

A) Cancel claim 56
B) Cancel claim 57
C) Cancel claim 58
D) Cancel claim 59

In the **Original Specification Disclosure**

E) Replace the paragraph starting **on page 3**, **line 7**, of the original specification with the following:

NMR microcoils are known to those skilled in the art and are shown, for example, in US patent 5,654,636 to Sweedler et al., and in US patent 5,684,401 to Peck et al., and in US patent 6,097,188 to Sweedler et al., all three of which patents are incorporated herein by reference in their entireties for all purposes. A solenoid microcoil detection cell formed from a fused silica capillary wrapped with copper wire has been used for static measurements of sucrose, arginine and other

simple compounds. Wu et al. (1994a), J. Am. Chem. Soc. 116:7929-7930; Olson et al. (1995), Science 270:1967-1970, Peck (1995) J. Magn. Reson. 108(B) 114124. Coil diameter has been further reduced by the use of conventional micro-electronic techniques in which planar gold or aluminum R.F. coils having a diameter ranging from 10-200 μm were etched in silicon dioxide using standard photolithography. Peck 1994 IEEE Trans Biomed Eng 41(7) 706-709, Stocker 1997 IEEE Trans Biomed Eng 44(11) 1122-1127, Magin 1997 IEEE Spectrum 34 51-61, which are also incorporated herein by reference in its entirety for all purposes. In Stocker et al. a microcoil was fabricated on a gallium arsenide substrate with an inner diameter of 60um, an outer diameter of 200 μm, trace width of 10 μm, trace spacing of 10 μm, and trace height of Sum. At 5.9T (250MHz) in 1H-NMR micro spectroscopy experiments using a spectral width of 1kHz, 4096 sampled data points, and a recovery delay of 1 s, a SNR of 25 (per acquisition) and a spectral line width of less than 2Hz were obtained from a sample of water.

F) **Replace** the paragraph starting on page 3, line 21, of the original disclosure with the following:

Miniature total analysis systems (μ-TAS) are discussed in Integrating Microfluidic Systems And NUR Spectroscopy - Preliminary Results, Trumbull et al, Solid-State Sensor and Actuator Workshop, pp. 101-05 (1998), Magin 1997 IEEE Spectrum 34 51-61, and Trumbull 2000 47(1) 1-6 incorporated herein by reference in its entirety for all purposes. These groups constructed chip-based capillary electrophoresis (CE) devices equipped with an integrated planar radio frequency detector coil used for nuclear magnetic resonance spectroscopy (NN R). Separations were accomplished in the devices, but satisfactory NMR spectra could only be obtained from samples of high concentration. Two prototype CE-NMR devices are presented that represent complete microanalytical instruments. Further, "The first system, Trident, was designed to be a proof-of-concept fluidic-

NMR device to gauge the effectiveness of integrated, single-turn planar NMR coils. The channel network was formed by solvent bonding a photopatterned polyimide coating (on a glass slide) with a cover-glass coated with a thin layer of polyimide. Holes were previously drilled ultrasonically in the glass slide to provide access. A lift-off process was used to create a 1 mm diameter, single-turn coil on the outer surface of the cover glass. The metal was formed from 3 evaporated layers: Cr/Cu/Cr with respective thicknesses of 150, 9700, and 150 angstroms for improved susceptibility matching. The resistance of the coil, pad to pad, was measured to be 5.9 0. Acrylic wells were then placed over the drilled holes and bonded with epoxy. The second device type created, SpinCollector shown in Fig. 1 blowups, was made from etched glass channels using methods developed from (D.J. Harrison and N. Chiem, "Immunoassay Flow Systems On-Chip," TRF, pp. 5-8., 1996). Annealed Pyrex glass wafers (1 mm thick) were etched in HF and HN03 to a depth of 20 μm through a Cr/Au mask. Access holes were drilled ultrasonically and. the mask was stripped. The wafers were then cleaned in a 1% HF bath for 1 minute with ultrasonic agitation to remove any loose glass particles. After thorough cleaning, the wafers were thermally bonded to unprocessed pieces forming closed channels. A 5 mm diameter, single-turn coil was then formed through lift-off on the undrilled cover-glass slide over the disk-shaped reservoir, and glass wells were attached using epoxy. The Trumbull et al. device integrated multiple chemical processing steps and the means of analyzing their results on the same miniaturized system. Specifically, Trumbull et al. coupled chip-based capillary electrophoresis (CE) with nuclear magnetic resonance spectroscopy (NMR) in a μ-TAS system.

G) **Replace** the paragraph starting on page 4, line 20, of the original disclosure with the following:

Capillary scale systems also are shown in United States patent No. 6,194,900, the entire disclosure of which is incorporated herein by reference for

all purposes. In such systems, a capillary-based analyte extraction chamber is connected to an NMR flow site, such as by being positioned as an operation site along a capillary channel extending to the NMR flow cell.

H) **Replace** the paragraph starting on page 5, line 3, of the original disclosure with the following:

Small volume flow probes are shown, for example, by Haner et al. in Small Volume Plow Probe for Automated Direct-Injection NAM Analysis: Design and Performance, J. Magn. Reson., 143, 69-78 (2000), the entire disclosures of which is incorporated herein by reference for all purposes. Specifically, Harter et al show a tubeless NMR probe employing an enlarged sample chamber or flowcell. In Haner et al., a 600 MHz, indirect detection NMR flow probe with a 120 μL active volume is evaluated in two configurations: first as a stand-alone small volume probe for the analysis of static nonflowing solutions, and second as a component in an integrated liquids-handling system used for high-throughput NMR analysis. Key advantages of the flowprobe include high molar sensitivity, ease of use in an automation setup, and superior reproducibility of magnetic field homogeneity, which enables the practical implementation of 1 D T2-edited analysis of protein-ligand interactions. Microcoil-based micro-NMR spectroscopy is disclosed in United States patent No. 5,654,636, United States patent No. 5,684,441, and United States patent No. 6,097,188, the entire disclosures of all of which are incorporated herein by reference for all purposes. Sample amounts can now range as small as several hundred microliters for conventional flowprobes to smaller than 1 μL for microcoil-based capillary-scale flowprobes. Acquisition times typically range from minutes to hours. The most expensive and technologically limiting component of the NMR system is the superconducting magnet. Although significant financial and technical investment has been made in the development of elaborate mechanical (robotic-controlled) sample changers and, more recently, automated flow injection systems for repetitive and

continuous sample throughput, the magnet remains today a dedicated component in which only sequential, one-at- a-time analysis of samples is carried out.

I) **Replace** the second paragraph starting on page 24, of the original disclosure with the following:

Li et al. (Li 1999 Anal. Chem. 71 4815-4820) describes a 4-coil assembly illustrative of certain aspects of the present disclosure. The solenoidal microcoils are mounted on horizontal (transverse to Bo) capillaries with a 90 degree rotation (x, y) and 5 mm vertical spacing between adjacent coils. Additional details of basic construction are known generally, as shown in the Li et al reference mentioned above. The Li et al. microcoils were fabricated using techniques previously described in detail (Olson et al., Anal. Chem. 70, pp.257A-264A, 1998, and Webb et al., J. Magn. Reson. B 113, pp. 83-87, 1996). A four-coil system was constructed for operation in a 250 MHz wide-bore (89mm) magnet; a two-coil system could be accommodated in either a narrow-bore (54mm) or wide-bore 500 MHz magnet. For the four-coil system, each coil was fabricated identically using 17 turns of 50 μm diameter copper wire with a 6 μm thick polyurethane coating (California Fine Wire, Grover Beach, CA) wrapped around a 355 μm outer diameter, 180 μm inner diameter polyimide-coated fused silica capillary (Polymicro Technologies, Phoenix, AZ), giving an observe volume (Vobs) of 28 nL. The microcoils were mounted one above the other with a vertical spacing of 5 mm between adjacent coils. Alternate coils were rotated 90° with respect to each other to reduce coupling. The whole system was surrounded by a container filled with FC-43. For the 2-coil system at 5010 MHz, the microcoils were constructed as described above, one on a 75 μm i.d. 360 μm o.d. capillary (Vobs = 5 nL) and the other on a 200 μm i.d. 360 μm o.d. capillary (Vobs = 31 nL). The coils were then mounted on double-sided printed circuit boards. The capillaries were oriented at the magic angle with respect to the BO field, and the

two boards attached back-to-back with copper shielding between the boards. The matching networks were designed to maximize the distance between the elements of the two circuits, with the microcoils separated by 5 mm transversely with respect to the BO field. The NMR probe modules disclosed here differ from such earlier devices in having multiple detectors, each having a detection site, i.e., as described above, void in the capillary microchannel to receive a test sample, and having an NMR microchannel aligned therewith.

J) **Replace** the first paragraph on page 26, of the original disclosure with the following:

The microchannels and associated NMR microcoils can be formed in a module, preferably a multi-layer substrate, such as a laminated multi-layer substrate, e.g., a selectively welded multi-layer substrate as disclosed in copending United States patent application Serial No. 60/239,010 filed on October 6, 2000, the entire disclosure of which is incorporated herein by reference for all purposes. Microlithographic microcoils can be employed in such laminate substrates, such as those disclosed in the above-mentioned US patent 5,684,401, the entire disclosure of which is incorporated herein by reference for all purposes. Alternatively, or in addition, one or more of the multiple NMR detector sites formed in the probe can be formed in a finger or peninsula-type extension of the substrate, and the microcoil can be formed as a separate 3-dimensional structure fitted over such substrate projection. It will be within the ability of those skilled in the art, that is, those skilled in this area of technology, given the benefit of this disclosure, to employ alternative suitable fabrication techniques for production of the multi- microcoil NMR detection probes disclosed here.

Examiner's Comment

Drawings

4. The examiner and the official draftsperson have approved the Formal Drawings submitted June 20th 2002. [See the attached PTO 948 Official Draftsperson's Review form which accompanies this action.]

Canceled Claims

5. **Claims 1-37,** and **40-55** are canceled as per applicant's May 24th 2004 supplemental after-final amendment response.

6. **Claims 56-59** are canceled as per the examiner's amendment of this office action, requested by applicant in the June 1st 2004, 4:50 pm telephonic interview to correct an oversight in the applicant's May 24th 2004 supplemental after-final amendment response, concerning **claims 56-59**.

The following is an examiner's Statement of **Reasons for Allowance**

7. With respect to **After-final claims 38**, and **39 of May 24th 2004, After-final Claims 38**, and **39** are considered to be **allowable over the prior art of record** because the prior arts of record do not teach or suggest an NMR probe with the combinational features of, **-A NMR probe module** comprising: among its features "at least one fluid inlet port, operative to receive a fluid sample, a fluid pathway comprising multiple channels in fluid communication with the at least one fluid inlet port for the transport of fluid sample to be tested; **multiple NMR detection sites, each in fluid communication with at least one of the multiple channels, each comprising: a sample holding void, and an associated NMR microcoil, wherein each NMR microcoil is operative to detect one or more analytes in the sample holding void with which the NMR microcoil is associated; a controllable fluid router operative to direct fluid sample in the module to at least a selected one of the multiple channels;** and an analyte extraction chamber in fluid communication with at least one of the NMR detection sites, wherein the analyte extraction chamber is **operative to**

perform dynamic field gradient focusing .(i.e. **claim 38**) or **electric field gradient focusing**.(i.e. **claim 39**).

8. It would not have been obvious to one of ordinary skill in the art at the time that the invention was made to construct an NMR probe, with each of the features as set forth in the allowed **claims 38** and **39**, because none of the prior arts of record have the entire combination of claimed features, with the controllable fluid router, the multiple detection sites, the multiple microcoils, with each microcoil being assigned to one of the multiple channels, and the functional ability to perform dynamic field gradient focusing (i.e. **claim 38**) or electric field gradient focusing (i.e. **claim 39**).

9. The prior arts of record, such as **Raftery et al.,** which have multiple channels and multiple NMR microcoils lack "the controllable fluid router operative to direct fluid sample in the module to at least a selected one of the multiple channels;" because in **Raftery et al., figure 8,** shows that each flow path is individually fixed, <u>there is no way to divert, or operationally select</u> (i.e. "controllably route") in **the prior art of record**, <u>the fluid of one channel to a selected one of the multiple channels, among alternatives, because there is no alternative path, option in the multichannel devices of the prior art of record</u>.

10. The difference is important because in the instant application the "controllable fluid router" which selects among the plurality of the multichannels of the NMR probe, is a separate component of the NMR probe, which provides the flexibility to control the flow of a fluid sample to one or more of the NMR probe's multichannels. In the instant invention the flow path is not fixed, in the invention Path A, is capable of leading to alternative channels including channel B, channel C, etc., or even more than one channel.

11. In **Raftery et al., Kucharczk et al., Freedman et al., Fisher et al.,** and **Webb et al.,** the fluid pathways are fixed, among the multichannels presented, such that path A = channel A; path B = channel B; path C = channel C; etc.,. automatically. There is no choice or differentiation in the prior art of record between the initial fluid path and the channel on which the NMR signal detection

occurs. The path which the fluid follows within the prior art devices does not and can not change, therefore, the path is not operationally selected / selectable by a controllable router, which is contrary to the claims of the instant invention. Because of the lack of a selectable choice between the fluid path and channel, there is no separate fluid router component in the prior art of record. Stated another way, in the prior arts of record, path A does not, and cannot lead to any other channel, within in the prior art devices. Because of this the **prior arts of record**, within their disclosed structures and teachings, each fail to provide, and in fact teach away from the structural feature of "a controllable fluid router operative to direct fluid sample in the module to at least a selected one of the multiple channels;" in combination with each of the other limitations of the allowable **claims 38**, and **39**, and it is the combination of all of the claim features in each of **claims 38** and **39** which when taken as a whole, are considered to be novel and nonobvious by the examiner.

12. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

13. The **prior art made of record** and not relied upon is considered pertinent to applicant's disclosure.

A) **Freedman et al.,** US patent 6194900 issued February 27th 2001, with an effective date of June 19th 1998. The examiner notes that this reference only has one microcoil, and lacks a "controllable fluid router operative to direct fluid sample in the module to at least a selected one of the multiple channels;".

B) **Fisher et al.,** PCT international application publication WO 00/50924 published August 31st 2000. The examiner notes that this reference fails to teach either the dynamic field gradient focusing (of **claim 38**) or the electric field gradient focusing (of **claim 39**).

C) **Webb et al.,** US patent 6,456,072 B1 issued September 24th 2002. The examiner notes that this reference fails to teach either the dynamic field gradient focusing (of **claim 38**) or the electric field gradient focusing (of **claim 39**).

D) **Kucharczk et al.,** US patent 6,026,316 issued February 15th 2000; with an effective date of May 15th 1997. The examiner notes that this reference fails to teach either the dynamic field gradient focusing (of **claim 38**) or the electric field gradient focusing (of **claim 39**).

E) **Raftery et al.,** US patent 6,696,838 B2 issued February 24th 2004, with an effective filing date of August 21st 2001, a US priority date from US PCT/US00/04842 of February 25th 2000, and a domestic US priority date from provisional application number 60/121,869 of February 26th 1999. The examiner notes that it is applicant's additional feature of the **controllable fluid router operative to direct fluid sample in the module to at least a selected one of the multiple channels; in combination with either the dynamic field gradient focusing** , (of **claim 38**) or the **electric field gradient focusing**, (of **claim 39**), in combination with each of the other features of these claims taken as a whole in combination with one another that distinguishes applicant's allowed claims from this prior art reference.

F) **Peck et al.,** US patent 6,700,379 B2 issued March 2nd 2004, filed December 3rd 2001. The examiner notes that this reference is not prior art against the claims of the instant application, because it has the same filing date as the instant application. The reference is relevant because three of the instant application's inventor's are also inventors of this patent. There is no double patenting because in the 6,700,379 B2 patent there is no "controllable fluid router operative to direct fluid sample in the module to at least a selected one of the multiple channels;", which is an aspect of each of applicant's allowed claims, therefore the instant application and this reference are considered to be distinct from one another. This reference is not available as prior art.

G) **Peck et al.,** US patent application publication 2002/0105327 A1 published August 8th 2002, filed December 3rd 2001, which is the corresponding Pre-grant

publication of US patent 6,700,379 B2 above. The examiner notes that this reference is not prior art against the claims of the instant application, because it also has the same filing date as the instant application. The reference is relevant because three of the instant application's inventor's are also inventors of this patent. There is no double patenting because in the 6,700,379 B2 patent and the patent application publication 2002/0105327 A1 there is no "controllable fluid router operative to direct fluid sample in the module to at least a selected one of the multiple channels;", which is an aspect of each of applicant's allowed claims, therefore the instant application and this reference are considered to be distinct from one another. This reference is not available as prior art.

H) **Peck et al.,** US patent application publication 2002/0149369 A1 published October 17th 2002, filed December 3rd 2001, which is the corresponding Pre-grant publication of applicant's instant application, and is noted only for the purposes of a complete record. This reference is not available as prior art.

Conclusion

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tiffany Fetzner whose telephone number is: (571) 272-2241. The examiner can normally be reached on Monday-Thursday from 7:00am to 4:30pm., and on alternate Friday's from 7:00am to 3:30pm.

15. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Diego Gutierrez, can be reached at (571) 272-2245. The **only official fax phone number** for the organization where this application or proceeding is assigned is **(703) 872-9306**.

Tiffany A. Fetzner

TAF
June 2, 2004

Diego Gutierrez
Supervisory Patent Examiner
Technology Center 2800